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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,481	WALDMAN ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64,65,68-75,91-103,132-135,140-143 and 146-165* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,65,68-75,91-103,132-135,140-143 and 146-165* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed April 21, 2008 in response to the Office Action of October 19, 2007 is acknowledged and has been entered. Previously pending claims 76-90, 136-139, and 144 have been cancelled, claims 64, 65, 68, 71- 75, 91-103, and 132-135 have been amended and new claims 146-165 have been added.

2. Applicants argue that in Applicants' Response to March 5, 2007 Restriction Requirement, Applicants believe an error was made in indicating that claim 70 read on the elected species. Specifically, Applicants indicated that claim 70 referred to the elected mode of administration. Applicants note that claim 71, not claim 70, reads on the elected mode of administration. Claim 70 reads on a non-elected different species of therapeutic agent. Applicants respectfully request that claim 71, which reads on the elected species be rejoined for examination at this time

Applicants' arguments have been considered and have been found persuasive and claim 71 will be rejoined for examination.

Additionally in view of Applicants amendments and the prior art the species of guanylyl cyclase C ligands and claim 73 will be rejoined for examination.

Claims 64, 65, 68-72, 74, 75, 91-103, 132-135, 140-143 and 146-165 are currently being examined.

Drawings

3. The drawings were received on 4/21/2008. These drawings are accepted.

Rejections Maintained

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 65, 68-70, 72, 74, 75, 91-103, and remain rejected and claims 71, 73, 145, and 147-165 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in section 8, pages 4-13 of the Office Action of October 19, 2007 .

In section 8 of the Office Action of October 19, 2007, Examiner argued:

One cannot extrapolate the teachings of the specification to the enablement of the claims because no nexus has been established between administering an antibody to the ST receptor to an individual and inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual and because 1) the artifactual nature of cell culture systems is well known in the art and 2) the development of therapeutics for malignant disorders such as colorectal cancer is well known in the art to be unpredictable

1) As drawn to the artifactual nature of cell culture systems in particular, it is well known in the art that the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine

systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al. (Clin. Can. Res., 1998, 4:1797-1802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). More recently, Zips et al (In vivo,

2005, 19:1-7) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro.* Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2). Additionally Clark et al. (US Pat. App. Pub. 20060019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the

hierarchy of cell populations that exist in vivo. Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109.

Thus, based on the cell culture data presented in the specification, in the absence of data demonstrating that antibody directed against the ST receptor can induce a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibit proliferation of primary or metastasized colorectal cancer cells in an individual in an appropriate *in vivo* model system, no one of skill in the art would believe it more likely than not that the invention would function as claimed, that is inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual, based only on the cell culture data provided.

2) As drawn to the unpredictability of drug development for malignant disorders such as cancer, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal

antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art recognizes that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the claimed method could be effectively used for inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col. 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col. 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer

cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col. 2). It is clear that based on the state of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that an antibody directed against the ST receptor could predictably be used in a method of inducing a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibiting proliferation of primary or metastasized colorectal cancer cells in an individual. In addition, anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established.

Given the above, in the absence of *in vivo* experimental data demonstrating induction of a cytostatic effect in primary or metastasized colorectal cancer cells in an individual or inhibition

of proliferation of primary or metastasized colorectal cancer cells in an individual with an antibody against the ST receptor or fragment thereof, one of skill in the art could not predict that the invention will function as claimed with a reasonable expectation of success

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as claimed based only on the information in the specification and that known in the art at the time the invention was made. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

Applicants argue that the *in vitro* experiments set forth in the specification accurately describe the mechanism by which guanylyl cyclase C effects cells, thereby allowing one skilled in the art to use such compounds to achieve the claimed effect in vivo. One skilled in the art would expect that the invention would be effective in vivo in view of the in vitro data. The cited art relied upon in the Official Action present a general case of questioning the extrapolation of in

vitro data to in vivo effectiveness. However, these references do not address specific instances where the mechanism for action is demonstrated at the level of detail and understanding set forth in the instant specification.

Applicants' arguments have been considered, but have not been found persuasive. Although the mechanism be which guanylyl cyclase C effects cells in vitro may be understood, given that no data is presented either *in vitro* or *in vivo* for any guanylyl cyclase C ligand/antibody that can *inhibit* the proliferation of a primary or metastasized colorectal cancer cell in an individual by the cytotostatic effect of guanylyl cyclase C, wherein the ligand *induces* proliferation of cells, undue experimentation would be required to practice the method as claimed.

Applicants argue that as for the predictability of antibody therapeutics, Applicants assert that at the time the invention was made, one skilled in the art would have accepted that the claimed subject matter would be effective. The references cited in the Official Action refer to the unpredictability of drugs with initial anti-cancer activity emerging as a clinically effective therapy. Applicants argue that there are many reasons for failures of anti-cancer drugs to become commercially useful products. The standards by which a drug is evaluated for commercial use is different from simply whether or not it is operable in the context of patent law. The mere failure of drugs to not proceed to commercialization does not indicate it does not work to the level needed to establish patentability. Thus, it is improper to rely on the statistics of failed drug development as supporting a rejection that the subject matter would not be enabled under the requirements of the patent law.

Applicants' arguments have been considered, but have not been found persuasive because Examiner is not requiring a showing of commercial success. The cited references show that the art of cancer therapeutics is unpredictable, thus given that no data is presented either *in vitro* or *in vivo* for any guanylyl cyclase C ligand/antibody that can *inhibit* the proliferation of a primary or metastasized colorectal cancer cell in an individual by the cytotostatic effect of guanylyl cyclase C, wherein the ligand *induces* proliferation of cells, undue experimentation would be required to practice the method as claimed.

Applicants' arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 149 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 149 recites the limitation "the method of claim" and does not recite the claim from which it dependes. There is insufficient antecedent basis for this limitation in the claim. Given that claims 148 and 150 depend from claim 103, it will be assumed for examination purposes that claim 149 also depends on claim 103.

7. Claim 65, 68-72, 74, 75, 91-103, 145, and 147-165 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation of inhibiting the proliferation of a primary or metastasized colorectal cancer by the cytotostatic effect of guanylyl cyclase C in an individual . . . wherein guanylyl cyclase C ligand molecules bind to guanylyl cyclase C on the surface of a primary or metastasized colorectal cancer cell and *induce proliferation* (emphasis added) of said cells. A review of the specification by the Examiner does not reveal support for a guanylyl cyclase C ligand molecule, antibody or otherwise, that both inhibits and induces proliferation of primary or metastasized colorectal cancer cells. The subject matter claimed in claims 65, 68-72, 74, 75, 91-103, 145, and 147-165 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 64 and 68-74 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,879,656 (Waldman March 9, 1999) as evidenced by Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157).

US Patent No. 5,879,656 teaches treating metastasized colorectal cancer with the guanylyl cyclase C (GCC) ligand uroguanylin (SEQ ID NO: 5) and related GCC ligands, see claims 1-3, and cols. 9 and 10. US Patent No. 5,879,656 teaches administering the compositions

of the invention to patients by infusion, see col. 17-lines 43-44. US Patent No. 5,879,656 teaches administering different therapeutic agents, such as 5-fluoruracil and bleomycin which are radio-stable, col. 13-lines 47-64, col. 25-lines 6-31 claims 5, 6 and 14. US Patent No. 5,879,656 teaches administering the ligands into the circulatory system, by intravenous injection, and directly into the tumor, see col. 7-lines 25-31, col. 17-lines 34-44 and claims 28, 29, 53, 54, 57, and 58. US Patent No. 5,879,656 teaches using antibodies to GCC with therapeutic agents for treatment, see col. 10-lines 44-47, col. 54-lines 46-58 and claims 38, 39, 48 and 49.

Shilubhai et al. (Cancer Research, Sep. 15, 2000 60:5151-5157) teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppress colon polyp formation, see Abstract, Fig. 2-4 and Table 1. Thus, uroguylin induces a cytotoxic effect through GCC.

Given that that the therapeutic agents taught by US Patent No. 5,879,656 are potent cytoxins, see col. 2-lines 10-15, given that the GCC antibodies conjugated to the therapeutic agents would be cytotoxic to the metastasized colorectal cancer cells, and in the absence of a limiting definition of "a therapeutic effect by the cytotoxic effect of the guanylyl cyclase C", the antibodies which bind GCC conjugated to therapeutic agents and radioisotopes of US Patent No. 5,879,656 would have "a therapeutic effect by the cytotoxic effect of the guanylyl cyclase C".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 75, 91-103, 132-135, 140-143, and 145-165 are rejected under 35 U.S.C. 103(a) as being unpatentable US Patent No. 5,879,656 (Waldman March 9, 1999), in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8), in further view of US Pat. No. 6,251,439 (Baron Jun. 26, 2001), in further view of Harlow and Lane (Antibodies, a Laboratory Manual, Cold Spring Harbor Laboratory Press, 1988, p. 141-142), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033), and in further view of Riechmann et al (Nature Vol 332:323-327 1988).

US Patent No. 5,879,656 teaches as set forth above and teaches using various doses of GCC ligand for treatment, such as 11 micrograms of ST-peptide conjugated compound/kg of

body weight (see cols. 18-20), but does not specifically teach the different doses and times of infusion of the GCC ligands, monoclonal antibodies to GCC or humanized monoclonal antibodies to GCC for use in the methods of US Patent No. 5,879,656 or administering calcium.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time (abstract).

US Pat. No. 6,251,439 (Baron Jun. 26, 2001) teaches a method for reducing the risk of colorectal adenoma, see claims and Example.

Harlow and Lane teach that the usefulness of monoclonal antibodies stems from three characteristics- their specificity of binding, their homogeneity, and their ability to be produced in unlimited quantities. The production of monoclonal antibodies allows the isolation of reagents with a unique, chosen specificity. Harlow and Lane teach that because all of the antibodies produced by descendants of one hybridoma cell are identical, monoclonal antibodies are powerful reagents for testing for the presence of a desired epitope. Harlow and Lane teach that hybridoma cell lines also provide an unlimited supply of antibodies, see p.141.

Queen et al teach a reproducible technique for making humanized antibodies (page 11030, col 2 para 3) and further teaches that for human applications humanized antibodies are more useful because of their reduced immunogenicity (page 10029, col 2, para 2).

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat antibody directed

against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use different doses and times of infusion of the GCC ligands, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

One of skill in the art would have been motivated to additionally administer calcium in combination with the methods of US Patent No. 5,879,656 for treating metastasized colorectal caner because US Pat. No. 6,251,439 teaches that calcium treatment reduces the risk of

colorectal adenoma development and one of skill in the art would be motivated reduce the risk of further cancer development to prevent further suffering of the patient using the combined methods. One of skill in the art would have a reasonable expectation of success as calcium has been successfully uses for the prevention of colorectal adenomas.

Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one of skill in the art would have been motivated to make monoclonal antibodies to the GCC ligand for use in the methods of US Patent No. 5,879,656 because Harlow and Lane teach the advantages of having an unlimited supply of homogeneous antibodies that have a defined specificity. Further, one of ordinary skill in the art would have been motivated to make humanized monoclonal antibodies with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by avoiding anti-isotypic antibodies.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 64, 68-73, 91-102, 132, 133, 135, 140-143, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 10, 11, 15-28, 33, and 36-39 of copending Application No. 11/166,592 in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8), and in further view of US Patent No. 5,879,656 (Waldman March 9, 1999).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application and the instant application are claiming common subject matter. The claims of both the copending application and the instant application are drawn to a method of treating an individual with esophageal and gastric/stomach cancer comprising administering a GCC ligand and active agent, wherein the ligand is conjugated to the agent and the agent kills or inhibits replication of cells.

US Patent No. 5,879,656 teaches treating metastasized colorectal cancer with the guanylyl cyclase C (GCC) ligand uroguanylin (SEQ ID NO: 5) and related GCC ligands conjugated to therapeutic moieties for delivery of the agents by targeting GCC, see claims 1-3, and cols. 9 and 10. US Patent No. 5,879,656 teaches administering the compositions of the invention to patients by infusion, see col. 17-lines 43-44. US Patent No. 5,879,656 teaches administering different therapeutic agents, such as 5-fluoruracil and bleomycin which are radio-stable, col. 13-lines 47-64, col. 25-lines 6-31 claims 5, 6 and 14. US Patent No. 5,879,656

teaches administering the ligands into the circulatory system, by intravenous injection, and directly into the tumor. col. 7-lines 25-31, col. 17-lines 34-44 and claim 28, 29, 53, 54, 57, and 58. US Patent No. 5,879,656 teaches using antibodies to GCC with therapeutic agents for treatment, see col. 10-lines 44-47, col. 54-lines 46-58 and claims 38, 39, 48 and 49.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use different doses and times of infusion of the GCC ligands taught by Application No. 11/166,592, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the GCC ligands conjugated to therapeutic agents and methods of delivery taught by US Patent No. 5,879,656 in combination with the GCC directed therapy of Application No. 11/166,592 to augment the therapeutic efficacy of the treatment given that both treatments are directed to treating GCC expressing cancer.

This is a provisional obviousness-type double patenting rejection.

11. Claims 64, 68-75, 91-102, 132-135, 140-143, 145 and 146 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-32, 35-38, 40-55, and 57-65 of copending Application No. 10/866,951 in view of Cohen (Int J Radiat Oncol Biol Phys, 1987, 13:251-8), in further view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033), and in further view of Riechmann et al (Nature Vol 332:323-327 1988).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application and the instant application are claiming common subject matter. The claims of both the copending application and the instant application are drawn to a method of treating an individual with esophageal cancer comprising administering a GCC ligand and active agent, wherein the ligand is and antibody or monoclonal antibody and is conjugated to the agent, wherein the agent is a chemotherapeutic, toxin, or radiosensitizing agent, wherein the agent inhibits cell division, wherein the agent is bleomycin or 5-FU, wherein the GCC ligand is administered by injection or intravenously. It is noted that the specification of Application No. 10/866,951 contemplates intratumor injection as a form of injection for administration, see page 44, lines 23-24 of 10/866,951.

Cohen teaches that to find the safest procedure for treating a tumor, one must search for that combination of factors which will maximize the conditional probability of controlling the tumor and avoiding injury in any normal tissues, this depends on several factors including dose, field-size, fractions, and time (abstract).

Queen et al teach a reproducible technique for making humanized antibodies (page

11030, col 2 para 3) and further teaches that for human applications humanized antibodies are more useful because of their reduced immunogenicity (page 10029, col 2, para 2).

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use different doses and times of infusion of the GCC ligands taught by 10/866,951, because Cohen teaches the best tumor treatment scheme is to maximize the chance of tumor control by optimizing factors such as dose and number of fractions and avoid complications. One would have been motivated to use different doses and times of infusion of the GCC ligands in order to optimize the dose needed to effectively treat the colorectal cancer

and to avoid complications such as injury to normal tissue. It is noted that optimum suitable ranges may be obtained by routine experimentation, absent a showing of criticality or unexpected results.

Additionally, one of ordinary skill in the art would have been motivated to make and use humanized forms of the monoclonal antibodies of 10/866,951with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful for reducing the anti-globulin responses during therapy by by avoiding anti-isotypic antibodies.

This is a provisional obviousness-type double patenting rejection.

12. All other objections and rejections recited in the Office Action October 19, 2007are withdrawn.

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642

/PJR/

/Karen A Canella/

Primary Examiner, Art Unit 1643